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Diagnosis and Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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CME Activity

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Learning Objectives: At the conclusion of this educational activity, the health care provider will be able to (1) diagnose myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in a patient, (2) formulate a work-up and treatment plan for a patient presenting with ME/CFS, and (3) identify and address common comorbidities and complications of ME/CFS.

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic neurologic disease often preceded by infection. There has been increased interest in ME/CFS recently because of its significant overlap with the post-COVID syndrome (long COVID or post-acute sequelae of COVID), with several studies estimating that half of patients with post-COVID syndrome fulfill ME/CFS criteria. Our concise review describes a generalist approach to ME/CFS, including diagnosis, evaluation, and management strategies.

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic neurologic disease often preceded by infection.[1] It is common and debilitating, with a prepandemic population-based prevalence of 1 to 2.5 million in the United States alone and a lower quality of life on average than multiple sclerosis,

chronic kidney failure, or congestive heart failure.[1-3] There has been increased interest in ME/CFS recently because of its significant overlap with the post-COVID syndrome (long COVID or post-acute sequelae of COVID), with several studies estimating that half of patients with post-COVID syndrome fulfill ME/CFS criteria.[4] Whereas the exact cause of ME/CFS is unknown, dysfunction in the neurologic, immunologic, endocrinologic, cardiovascular, and metabolic systems has been found in people with ME/CFS and post-COVID syndrome.[1,4-6] Research is underway to identify diagnostic markers and therapeutic targets.

The pathognomonic symptom of ME/CFS is post-exertional malaise (PEM) or post-exertional symptom exacerbation. Post-exertional malaise is a flare in symptoms or the appearance of new symptoms after exertion, often manifesting after a characteristic 24-hour delay; however, 12 to 48 hours is common. Physical activity, cognitive overexertion, and sensory overload may all trigger PEM. It may take a person with ME/CFS days, weeks, or even months to return to previous baseline after PEM.[1,7]

It has been reported that patients with ME/CFS have impaired oxygen extraction on cardiopulmonary exercise testing in proportion to the severity of their symptoms, with both oxygen extraction and workload being decreased on the second day of 2-day cardiopulmonary exercise testing.[8,9] This reflects and may in part explain the characteristic delay between exertion and PEM onset in ME/CFS and distinguishes patients from deconditioned and fatigued controls.[8] However, we do not recommend routine exercise testing for patients with ME/CFS, given its propensity to generate PEM and to decrease functional capacity.

EPIDEMIOLOGY/ETIOLOGY

Myalgic encephalomyelitis/chronic fatigue syndrome affects people of all ages, genders, races, and socioeconomic backgrounds but is more frequently reported in women.[1] There is some evidence that ME/CFS presentation may differ in men compared with women, leading to underdiagnosis in men.[10] The prevalence of ME/CFS among transgender and gender-diverse people has not been thoroughly studied.

Although all racial backgrounds show comparable prevalence, Black, indigenous, and people of color are less likely to be diagnosed.[11,12] The source of this discrepancy is unclear, but access issues, poorer health status of underserved ethnic groups, and assumptions around racial prevalence have been suggested. Epidemiologic studies found a bimodal distribution of diagnosis between ages 10 to 19 and 30 to 39.[13] In adults with ME/CFS, symptoms may have initially appeared in childhood, remitted, then returned in adulthood.

Myalgic encephalomyelitis/chronic fatigue syndrome has been associated with antecedent infection, often viral, in up to 80% of cases.[1] Outbreaks of epidemic ME/CFS have been documented after Epstein-Barr virus and other herpesviruses (HHV-6, HHV- 7), cytomegalovirus, enterovirus, and coronavirus infections including SARS-CoV-2, among other pathogens.[1,4,14] Punctuated onset with multiple triggering events initiating minor symptoms, followed by a final trigger leading to overt onset, is also common. It may also be initiated by other physiologic stressors, such as surgery, trauma, or other immunologic perturbations.[1]

DIAGNOSIS

The Centers for Disease Control and Prevention recommend the 2015 Institute of Medicine/National Academy of Medicine criteria to diagnose ME/CFS, although other criteria have been proposed (Figure 1). Diagnosis of ME/CFS is based on positive signs and symptoms and is therefore not a diagnosis of exclusion.[1,7] It is estimated that up to 90% of people with ME/CFS are yet undiagnosed, and 29% of those who have been diagnosed waited 5 years or more to receive an accurate diagnosis.[1,7] This may be due to the lack of a reliable diagnostic biomarker, heterogeneity in clinical presentation across patients and time that may mimic the presentation of other diseases, and suboptimal clinician awareness of the condition.[1]

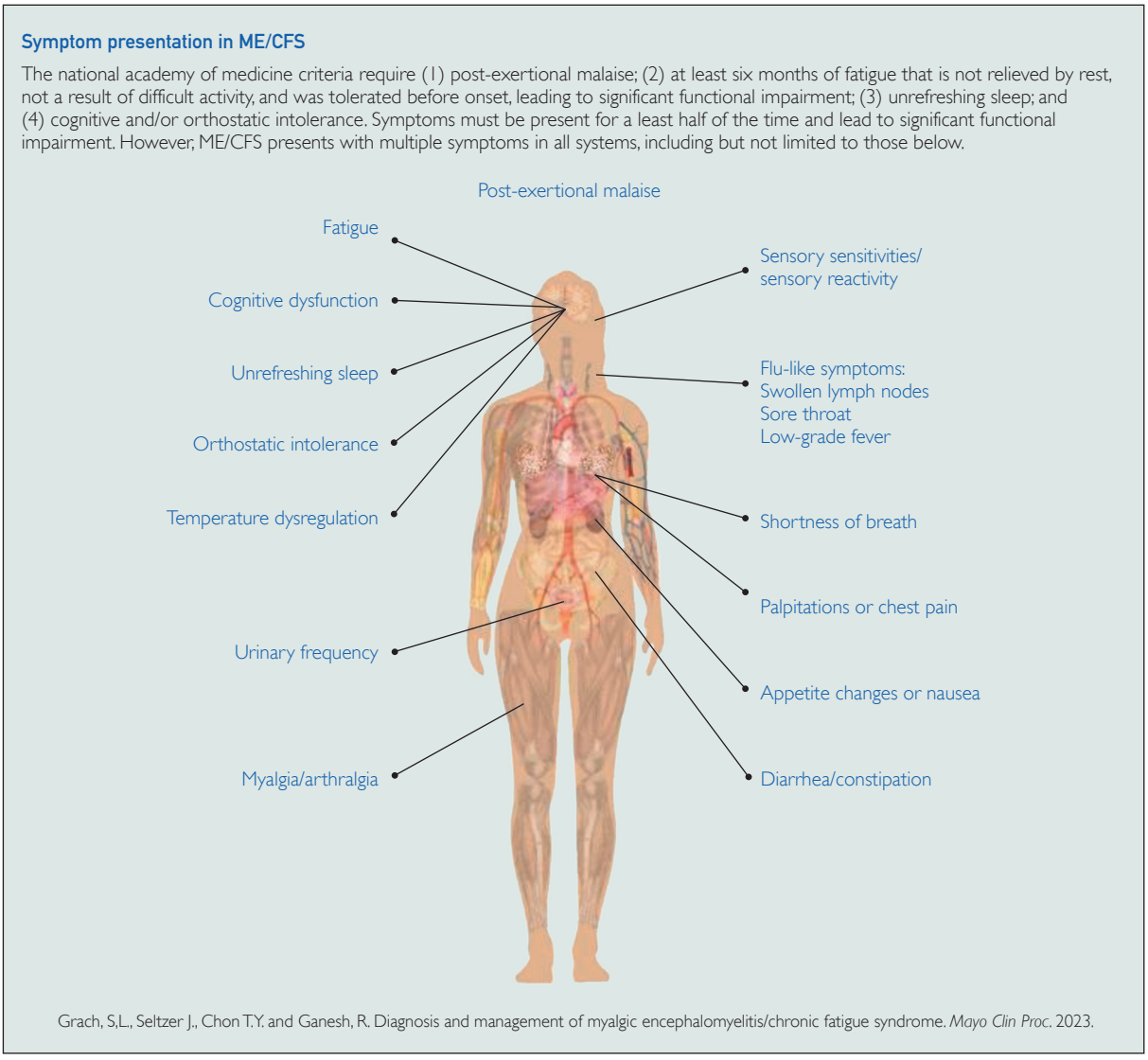

FIGURE 1. Sympton presentation in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Myalgic encephalomyelitis/chronic fatigue syndrome may be manifested as mild, moderate, severe, or very severe. Patients with mild disease may work or attend school but must often reduce other activities to do so; a 50% decrease from preillness levels of function is often used with the Institute of Medicine/National Academy of Medicine criteria for diagnosis. About 25% of cases are considered mild, 50% are considered moderate to moderate-severe (reduced capacity for mobility and activities of daily living), and 25% are estimated to be severe (housebound) or very severe (bedbound).[15]

PRACTICAL APPROACH TO RECOGNITION AND DIAGNOSIS

Patient History

Post-exertional malaise is the pathognomonic symptom of ME/CFS and is required for the current criteria used for diagnosis

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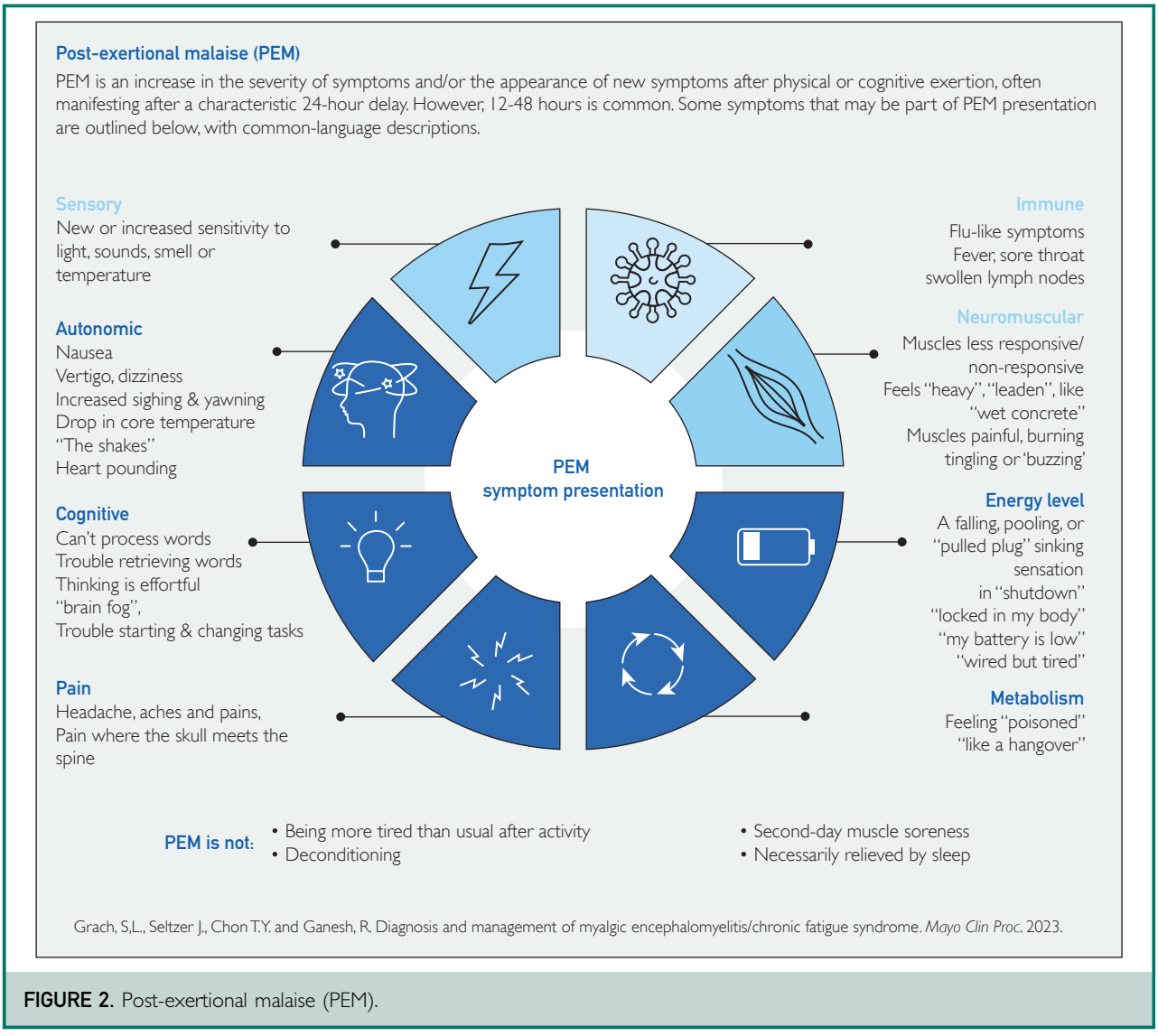

FIGURE 2. Post-exertional malaise (PEM).

to be met (Figure 2). In addition, patients must also present with fatigue, unrefreshing sleep, and orthostatic intolerance or cognitive impairment. However, most patients present with multiple additional symptoms in multiple systems. These symptoms must have been severely impairing and present for 6 months or more.[1,5,7]

Risk Factors

It is generally accepted that risk factors for development of ME/CFS include female sex; age (with peaks in adolescence and in the third decade of life); infection, especially viral infection, before onset; and preexisting or family history of autoimmune disease, neurologic disease, or other multisystem chronic complex diseases.[13,16]

PHYSICAL EXAMINATION

There is currently no physical examination finding that is specifically associated with ME/CFS. Clinicians may be able to elicit painful lymph nodes or tender points similar to and even potentially meeting criteria for fibromyalgia, which is a common comorbid condition.[5] Abdominal tenderness without rebound or guarding may also be noted, especially when irritable bowel syndrome coexists. Joint examination may be positive

*Adrenocorticotropic hormone stimulation test and endocrine evaluation can be pursued if cortisol level is markedly abnormal. Insulin tolerance testing may be ordered by subspecialist if adrenocorticotropic hormone stimulation test results are inconclusive.

for hypermobility and cervical facet joint tenderness (particularly at the base of the skull); however, active synovitis on joint examination should raise concern for contributing rheumatologic disease. A mental status examination or close attention to responses to clinician questions may reveal transient difficulties with word finding, memory, or other cognitive processing. If it is able to be performed, orthostatic testing in the office by the NASA lean test can reveal symptoms of orthostatic intolerance with or without accompanying hypotension.[5] However, despite regularly experiencing substantial debilitation, patients often come to the clinic only when they are functionally able and so may simply present fatigued but otherwise well on evaluation.[7]

DIFFERENTIAL DIAGNOSIS AND COMORBIDITIES

Comorbid Disorders

Identification of treatable comorbidities can be vital to improving patients' quality of life.[5] As in many other postinfectious neurologic diseases, people with ME/CFS may have a family history of associated conditions[2]; 75% to 80% of patients with ME/CFS report a diagnosis of at least 1 other disease or disorder.[17] Other chronic complex diseases commonly diagnosed in people with ME/CFS include hypermobile Ehlers-Danlos syndrome; disorders of autonomic function, often manifesting as postural orthostatic tachycardia syndrome; and mast cell activation syndrome.[6,18] Patients with severe ME/CFS are likely to have a greater number of comorbidities, further complicating diagnosis and treatment.[15]

Evaluation

All patients in whom ME/CFS is suspected should undergo basic laboratory evaluation to assess for confounding or exacerbating conditions.[7] The following tests are required on referral to the Mayo Clinic Fibromyalgia and Chronic Fatigue Syndrome Clinic:

- Complete blood count with differential
- Comprehensive metabolic panel
- Ferritin
- Vitamin D
- Vitamin B_{12} and folate
- Thyroid function testing
- Erythrocyte sedimentation rate and C-reactive protein
- Cortisol and dehydroepiandrosterone sulfate*
- Phosphorus
- Antinuclear antibody
- Rheumatoid factor
- Tissue transglutaminase celiac testing
- Urinalysis
- Overnight oximetry

If orthostasis symptoms are present, an autonomic reflex screen (including 10-minute tilt table) may be advised. In the event that this testing is not available, an in-office NASA lean test may be used to identify and to characterize orthostatic intolerance and possible postural orthostatic tachycardia syndrome.[5,7]

Further Investigation/Specialist Referral

For a list of validated diagnostic instruments used in ME/CFS, see the National Institute of Neurological Disorders and Stroke Common Data Elements Project.[19] Once a diagnosis of ME/CFS has been established, patients should be counseled on tailoring their energy expenditure through the principles of symptom-contingent pacing to reduce the risk of PEM exacerbation. We also encourage the use of common pharmacologic options by primary care professionals. If basic management approaches are not sufficient in improving symptoms, it is recommended that patients be referred to an ME/CFS specialist for further management.

GENERAL MANAGEMENT

A general approach to management of ME/CFS based on common symptoms is highlighted in the Table. Health care professionals with access to AskMayoExpert are encouraged to use the ME/CFS algorithm for a more interactive and detailed approach to management[20]; ME/CFS or system-specific specialist consultation may be helpful for additional considerations. Symptom-

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TABLE. Management considerations for ME/CFS based on symptoms.

Symptom	Management considerations
Post-exertional malaise	Pacing/rest, stimulus reduction, tracking devices or diaries for symptoms
Fatigue	Pacing, low-dose naltrexone, low-dose aripiprazole, anti-inflammatory diets, supplements, vitamin deficiency treatment
Sleep issues	Melatonin, trazodone, suvorexant, doxepin/tricyclic antidepressants, gabapentin/pregabalin
Cognitive dysfunction	Journaling, memory aids, occupational therapy, low-dose naltrexone, low-dose aripiprazole, careful use of stimulants
Orthostatic intolerance	Fluids/electrolytes/compression, fludrocortisone, midodrine, propranolol, pyridostigmine, guanfacine (best guided by postural orthostatic tachycardia syndrome subtype or tilt vital signs)
Dizziness (frequent)	Consider persistent postural-perceptual dizziness diagnosis, vestibular therapy, low-dose selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor
Muscle or joint pain	Over-the-counter medications, duloxetine, milnacipran, pregabalin, gabapentin, tricyclic antidepressants, low-dose naltrexone
Neuropathy	Pregabalin, gabapentin, tricyclic antidepressants, compression or brace therapy
Sensory amplification	Noise-canceling headphones, tinted glasses, crowd exposure reduction, low-dose aripiprazole
Gastrointestinal symptoms	Anti-inflammatory diets, small meals, pro/synbiotics, antidiarrheals or antihistamines for diarrhea, fiber or motility agents for constipation

contingent pacing is recommended to all patients with ME/CFS. Pacing is a self-management strategy for activity wherein patients are active when able and rest when tired. They may plan extra rest ahead of strenuous activities. The goal of pacing is to avoid PEM exacerbation. Patients who learn to pace will often gain functional capacity. However, pacing does not involve systematic increases in activity over time; it is not intended to be curative or rehabilitative but a strategy used to manage symptoms and to improve quality of life. Patients may benefit from closely monitoring their physical and cognitive exertion using a symptom and activity diary or a wearable device. It may also be useful to ask them to keep track of their hours of upright activity, which includes sitting with feet on the floor. Graded exercise therapy has not been proven to be beneficial in ME/CFS and is therefore not recommended.[5,7]

A symptom diary can help patients identify activities that lead to PEM, and a wearable device can ensure that objective values were recorded when engaged in those activities. Monitoring activity to ensure that heart rate stays below that value can help prevent or mitigate PEM. Some devices can be programmed to alert the wearer when the heart rate reaches a certain value so that patients can decrease activity in time to prevent PEM. If patients continue to experience PEM, they may have to decrease activity until it no longer induces PEM. Likewise, they may be able to increase their "safe" heart rate if they do not experience PEM.[5]

In the event of PEM, patients should be urged to reduce their activity and to decrease exacerbating sensory stimuli. Patients with ME/CFS should rest to recover rather than pushing through exacerbated symptoms. Several specialty organizations for people with ME/CFS, such as the #MEAction Network and Bateman Horne Center, have published materials on pacing and supporting patients through PEM. Common at-home therapies include increasing fluid and electrolyte intake to counteract orthostatic intolerance, reducing stimuli in the room, and using assistive devices to minimize energy expenditure during limited activity.[5] Patients in very severe episodes presenting to the emergency department or hospital may benefit from intravenous administration of saline and electrolyte repletion.[21]

Many patients with ME/CFS use supplements because of medication sensitivity or

lack of pharmacologic options offered by medical professionals. Metabolic intermediates, such as coenzyme Q10, reduced form of nicotinamide adenine dinucleotide, L-arginine, or omega-3 fatty acids such as EPA or DHA, which have been used to address minor cognitive impairment in other neurologic diseases, may be trialed.[7,22] Supplements with immunologic or anti-inflammatory properties, such as lactoferrin, quercetin, and curcumin, may also be helpful. Clinicians should also treat vitamin and mineral deficiencies if present.

Pharmacologic management options for symptoms of ME/CFS are available and may be recommended on the basis of the patient's primary symptoms. As patients may experience medication intolerance at regular doses, treatment strategies generally follow the principle of "start low and go slow."[5] Regarding ME/CFS-specific therapies, studies suggest a benefit in particular from low-dose forms of medications such as pyridostigmine, aripiprazole, and naltrexone for fatigue.[5,21,23,24] Stimulant medications such as modafinil or methylphenidate may help fatigue and brain fog but risk worsening hyperadrenergic symptoms and PEM, and so should be employed with care.

Most people with ME/CFS will be diagnosed with at least 1 comorbid condition.[17] However, symptoms may be addressed with similar therapeutic approaches with or without official comorbid diagnosis. For example, patients with orthostatic intolerance or widespread pain symptoms may benefit from therapies directed to postural orthostatic tachycardia syndrome or fibromyalgia, respectively. The most appropriate orthostatic therapies are determined by subtyping. Examples of medications include propranolol or ivabradine for hyperadrenergic symptoms, fludrocortisone or midodrine for low blood pressure, and pyridostigmine for neuropathic subtypes. Food and Drug Administration–approved medications for fibromyalgia include duloxetine, milnacipran, and pregabalin. Sleep medications that have been associated with symptom relief in fibromyalgia, such as trazodone and suvorexant, may also help insomnia in ME/CFS. Doxepin or other antihistamine-based therapies may be tried for sleep in cases that are thought to also involve mast cell activation syndrome.[5,24] For more in-depth information about pharmacologic treatment options, we recommend that interested health care professionals view the ME/CFS Treatment Recommendations document published by the US ME/CFS Clinician Coalition.[24]

Malabsorption and malnutrition due to gastrointestinal and immunologic disease are common in severe-presenting patients. Anorexia nervosa is often incorrectly diagnosed in these patients, especially when presenting with malabsorption. Parenteral nutrition may be required; in such cases, refeeding syndrome should be considered.[15] Patients with severe ME/CFS may also require gastric tube feeding and intravenous administrations to avoid critical electrolyte imbalances, requiring total care in compatible homes or in nursing facilities.[25]

CONCLUSION

Myalgic encephalomyelitis/chronic fatigue syndrome is a chronic neurologic disease affecting millions of people in the United States. The disease is characterized most distinctively by its pathognomonic symptom, PEM. It is heterogeneous in cause and may be encountered in isolation or in association with 1 of multiple common comorbid conditions. Physical examination may be notable for lymph node, muscle, or abdominal tenderness; joint hypermobility; and word-finding difficulty or other cognitive impairment. All patients should be counseled on the importance of energy allocation through symptom-contingent pacing rather than graded exercise therapy. Complex cases that cannot be managed at the primary care level may be referred to an ME/CFS specialty clinic for additional evaluation and management.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

Abbreviations and Acronyms: **ME/CFS**, myalgic encephalomyelitis/chronic fatigue syndrome; **PEM**, post-exertional malaise

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